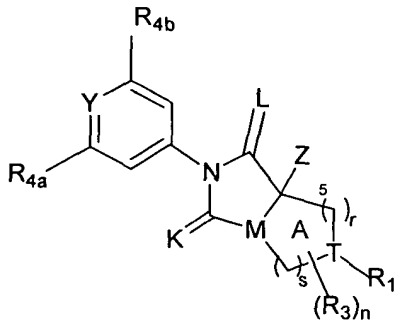
CLAIMS

We claim:

1. A compound having the formula (I),



(I)

or a pharmaceutically-acceptable salt thereof, in which:

L and K, taken independently, are O or S;

M is N or CH;

Y is CH or N;

Z is hydrogen, alkyl, or substituted alkyl, provided that Z may be selected from arylalkyl and heteroarylalkyl only when M is CH and/or when A has a second ring fused thereto;

T is nitrogen, CH, or a carbon atom substituted with an R_3 group;

R_1 is Q-aryl or Q-heteroaryl, wherein (a) when T is not nitrogen, Q is selected from a bond, -O-, -NR_{10}-, -S-, -C(=O)-, -CO_2-, -OC(=O)–, -NR_{10}C(=O)-, -C(=O)NR_{10}-, -$NR_{10}CO_2$-, C_{1-4}alkylene, C_{1-4}substituted alkylene, C_{1-4}alkenylene, C_{1-4}substituted alkenylene, and optionally-substituted bivalent C_{1-4}alkoxy, C_{1-4}alkylthio, C_{1-4}alkylamino, C_{1-4}aminoalkyl, C_{0-4}alkylsulfonyl, C_{0-4}alkylsulfonamide, C_{1-4}acyl, or C_{1-4}alkoxycarbonyl, or when Z is arylalkyl or heteroarylalkyl, R_1 may join with an R_3 group to form a fused carbocyclic or heterocyclic ring; or (b) when T is nitrogen, then Q is selected from a bond, -C(=O)-, -CO_2-, -OC(=O)–, -C_{1-4}alkylene, C_{1-4}substituted alkylene, C_{1-4}alkenylene, C_{1-4}substituted alkenylene, or optionally-substituted bivalent C_{1-4}alkoxy, C_{1-4}alkylthio, C_{1-4}aminoalkyl, C_{0-4}alkylsulfonyl, C_{0-4}alkylsulfonamide,

C_{1-4}acyl, or C_{0-4}alkoxycarbonyl, provided that when M is N, T is N, *r* is 1, and *s* is 2 such that ring A is piperazine, R_1 is not an amine-protecting group;

R_3 is selected from (i) a substituent R_3, wherein each substituent R_3 is individually attached to any available carbon or nitrogen atom of ring A and at each occurrence is selected independently of each other R_3 from halogen, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, OR_8, NR_8R_9, CO_2R_8, $(C=O)R_8$, $C(=O)NR_8R_9$, $NR_8C(=O)R_9$, $NR_8C(=O)OR_9$, $OC(=O)R_8$, $OC(=O)NR_8R_9$, SR_8, $S(O)_qR_{8a}$, $NR_8SO_2R_9$, $SO_2NR_8R_9$, aryl, heteroaryl, heterocyclo, and cycloalkyl, and when attached to an atom of ring A other than T, R_3 is optionally keto (=O), provided that when R_3 is attached to the atom designated as the C-5 atom of ring A, then R_3 is not aryl or heteroaryl, and (ii) a first group R_3 and a second group R_3, wherein the first group R_3 and the second group R_3 are attached to two adjacent atoms of ring A and together form an optionally-substituted carbocyclic or heterocyclic ring fused to ring A;

R_{4a} and R_{4b} are selected independently of each other from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, hydroxy, alkoxy, substituted alkoxy, phenyloxy, benzyloxy, CO_2H, C(=O)H, amino, alkylamino, substituted alkylamino, CO_2alkyl, (C=O)alkyl, and alkylthio;

R_8 and R_9 (i) selected independently of each other are hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, aryl, heteroaryl, or heterocyclo; or (ii) taken together form a heterocyclo ring;

R_{8a} is alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclo;

R_{10} is hydrogen, alkyl, or substituted alkyl;

n is 0, 1, or 2;

q is 1, 2, or 3;

r is 1 or 2; and

s is 0, 1, or 2.

2. The compound of claim 1, or a pharmaceutically-acceptable salt thereof, wherein:

at least one of L and K is O;

Y is CH;

Z is hydrogen, lower alkyl, or lower alkyl substituted with hydroxy, alkoxy, halogen, cyano, nitro, amino, or alkylamino;

T is nitrogen, CH, or CR_{3a} wherein R_{3a} is hydroxy, amino, alkylamino, halogen, cyano, or C_{1-4} alkyl optionally substituted with hydroxy, amino, alkylamino, halogen, or cyano;

R_1 is Q-aryl or Q-heteroaryl, wherein (a) when T is not nitrogen, Q is selected from a bond -O-, $-NR_{10}-$, -S-, -C(=O)-, $-CO_2-$, -OC(=O), C_{1-4}alkylene, C_{1-4}substituted alkylene, C_{1-4}alkenylene, C_{1-4}substituted alkenylene, or optionally-substituted bivalent C_{1-4}alkoxy, C_{1-4}alkylthio, C_{1-4}alkylamino, C_{1-4}aminoalkyl, C_{0-4}alkylsulfonyl, C_{0-4}alkylsulfonamide, C_{1-4}acyl, and C_{0-4}alkoxycarbonyl; or (b) when T is nitrogen, then Q is selected from a bond, -C(=O)-, $-CO_2-$, -OC(=O), $-C_{1-4}$alkylene, C_{1-4}substituted alkylene, C_{1-4}alkenylene, and C_{1-4}substituted alkenylene;

R_3 is attached to any available carbon atom of ring A other than T and is selected from halogen, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, OR_8, NR_8R_9, CO_2R_8, $(C=O)R_8$, $C(=O)NR_8R_9$, $NR_8C(=O)R_9$, $NR_8C(=O)OR_9$, $OC(=O)R_8$, $OC(=O)NR_8R_9$, SR_8, $S(O)_qR_{8a}$, $NR_8SO_2R_9$, $SO_2NR_8R_9$, aryl, heteroaryl, heterocyclo, cycloalkyl, and keto (=O), provided that when R_3 is attached to the atom designated as the C-5 atom of ring A, then R_3 is not aryl or heteroaryl;

R_{4a} and R_{4b} are selected independently of each other from the group consisting of hydrogen, halogen, alkyl, alkoxy, cyano, nitro, haloalkyl, and haloalkoxy;

R_8 and R_9 selected independently of each other are hydrogen or alkyl, and R_{8a} is alkyl;

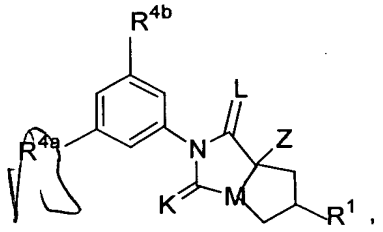
R_{10} is hydrogen, lower alkyl, or lower alkyl substituted with CO_2H or CO_2alkyl;

n is 0 or 1;

r is 1; and

s is 1 or 2.

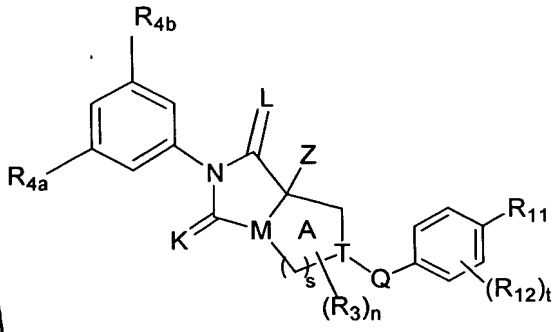
3. A compound according to claim 1 having the formula:



or a pharmaceutically-acceptable salt thereof.

4. A compound according to claim 1, or a pharmaceutically-acceptable salt thereof, in which R_1 is -O-C_{0-2}alkylene-phenyl, -S-C_{0-2}alkylene-phenyl, -NR_{10}-C_{0-2}alkylene-phenyl, -C_{1-3}acyl-phenyl, -C_{0-2}alkoxycarbonyl-phenyl, or -NR_{10}-SO_2-phenyl, and said R_1 phenyl group has zero to two substituents selected from halogen, C_{1-4}alkyl, nitro, cyano, hydroxy, C_{1-4}alkoxy, haloalkyl, haloalkoxy, CO_2H, C(=O)H, amino, C_{1-4}alkylamino, CO_2C_{1-4}alkyl, (C=O)C_{1-4}alkyl, C_{1-4}alkylthio, phenyl, phenyloxy, benzyl, or benzyloxy.

5. A compound according to claim 1, having the formula,



or a pharmaceutically-acceptable salt thereof, wherein:

Z is hydrogen, alkyl, or alkyl substituted with hydroxy, alkoxy, halogen, cyano, nitro, amino, or alkylamino;

R_{11} is hydrogen, halogen, alkyl, alkoxy, haloalkyl, haloalkoxy, nitro, or cyano;

R_3 and R_{12} are independently selected from alkyl, substituted alkyl, halogen, haloalkyl, haloalkoxy, nitro, cyano, hydroxy, alkoxy, amino, alkylamino, acyl, alkoxycarbonyl, carbamyl, sulfonyl, and sulfonamide;

n is 0 or 1;

s is 1 or 2; and

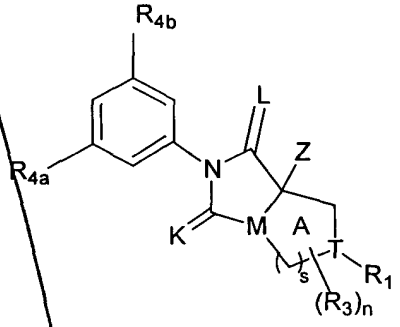
t is 0, 1, or 2.

6. The compound of claim 1, or a pharmaceutically-acceptable salt thereof, in which R_{4a} and R_{4b} are both halogen.

7. The compound of claim 1, or a pharmaceutically-acceptable salt thereof, in which M is CH.

8. The compound of claim 1, or a pharmaceutically-acceptable salt thereof, wherein M is N, T is N, *r* is 1 and *s* is 2 such that ring A is piperazine, and R_1 is Q-aryl or Q-heteroaryl wherein Q is selected from a bond, -C(=O)-, -CO_2-, -OC(=O)-, -C_{1-4}alkylene, C_{1-4}substituted alkylene, C_{1-4}alkenylene, and C_{1-4}substituted alkenylene, provided that Q-R_1 is not benzyl or carbobenzyloxy.

9. A compound having the formula (Ia),



(Ia)

or a pharmaceutically-acceptable salt thereof, in which:

L and K are O or S;

M is N or CH;

Z is hydrogen, alkyl, alkyl substituted with hydroxy, halogen, cyano, amino, or alkylamino; or when R_1 together with an R_3 group join to form a benzo ring fused to ring A, Z is arylalkyl or heteroarylalkyl;

T is nitrogen or CR_5;

R_1 is (a) –W-$(CH_2)_m$-Ar, or (b) taken together with an R_3 group to form a benzo ring fused to ring A, in which case Z is arylalkyl or heteroarylalkyl;

Ar is aryl or heteroaryl substituted with zero or one R_{11} and zero to two R_{12} groups;

W is selected from (a) when T is CR_5, a bond, -O-, -NR_{10}-, -S-, -C(=O)-, -CO_2-, and -CH(R_{13})-C(=O)-; and (b) when T is nitrogen, a bond, -C(=O)-, -

CO_2-, and -CH(R_{13})-C(=O)-, provided that when M is N, T is N, and *s* is 2 such that ring A is piperazine, then W-$(CH_2)_m$-Ar is not benzyl or carbobenzyloxy;

R_3 is selected from (i) a substituent R_3, wherein each substituent R_3 is individually attached to any available carbon or nitrogen atom of ring A and at each occurrence is selected independently of each other R_3 from halogen, alkyl, substituted alkyl, alkenyl, nitro, cyano, keto (=O), OR_8, NR_8R_9, CO_2R_8, $(C=O)R_8$, $C(=O)NR_8R_9$, $NR_8C(=O)R_9$, $NR_8C(=O)OR_9$, $OC(=O)R_8$, $OC(=O)NR_8R_9$, SR_8, $S(O)_qR_{8a}$, $NR_8SO_2R_9$, $SO_2NR_8R_9$, aryl, heteroaryl, heterocyclo, and cycloalkyl; and (ii) a first group R_3 and a second group R_3, wherein the first group R_3 and the second group R_3 are attached to two adjacent atoms of ring A and together form an optionally-substituted carbocyclic or heterocyclic ring fused to ring A, or one R_3 together with R_1 may join to form a fused benzo ring;

R_5 is hydrogen, halogen, alkyl, alkenyl, hydroxy, nitro, cyano, hydroxy, alkoxy, amino, or alkylamino, or C_{1-4} alkyl optionally substituted with hydroxy, amino, alkylamino, halogen, or cyano;

R_{4a} and R_{4b} are selected independently of each other from the group consisting of hydrogen, halogen, alkyl, nitro, cyano, haloalkyl, and haloalkoxy;

R_8 and R_9 (i) selected independently of each other are hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclo; or (ii) taken together form a heterocyclo ring;

R_{8a} is alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclo;

R_{11} is hydrogen, halogen, alkyl, hydroxy, alkoxy, amino, alkylamino, haloalkyl, haloalkoxy, nitro, or cyano;

R_{12} is alkyl, substituted alkyl, halogen, haloalkyl, haloalkoxy, nitro, cyano, hydroxy, alkoxy, substituted alkoxy, amino, alkylamino, acyl, alkoxycarbonyl, carbamyl, sulfonyl, or sulfonamide;

R_{10} and R_{13} are independently hydrogen, alkyl, or substituted alkyl;

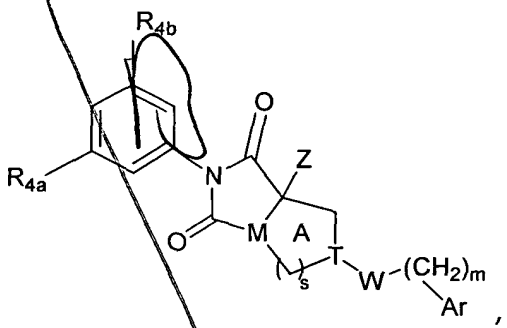
m is 0, 1, 2, 3, or 4;

n is 0, 1 or 2;

q is 1, 2, or 3; and

s is 1 or 2.

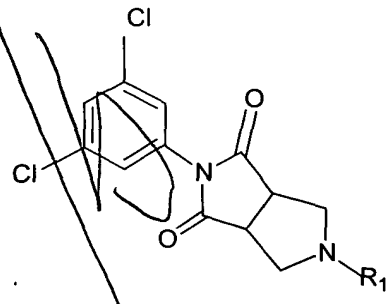
10. A compound according to claim 9, having the formula:



or a pharmaceutically-acceptable salt thereof.

11. A compound according to claim 10, in which Ar is optionally substituted phenyl or isoquinolinyl and R_{4a} and R_{4b} are both halogen.

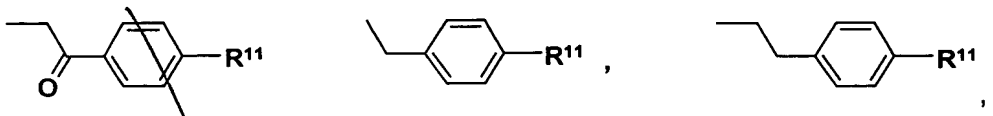
12. A compound according to claim 9 having the formula (Ia),



(Ia)

in which

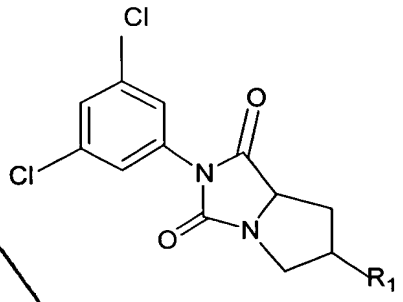
R_1 is selected from



and

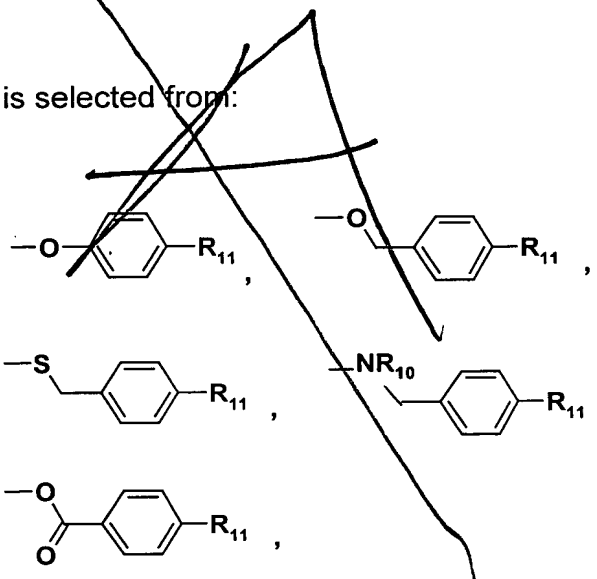
R_{11} is selected from hydrogen, bromo, chloro, cyano, and methoxy.

13. A compound according to claim 9 having the formula (Ib),



(Ib)

in which R_1 is selected from:



;

R_{11} is selected from hydrogen, bromo, chloro, cyano, and methoxy, and R_{10} is selected from hydrogen and alkyl.

14. A compound according to claim 9 which is: (I) (7aS,6S)-2-(3,5-dichloro-phenyl)-6-(4-bromophenoxy)-tetrahydro-pyrrolo[1,2-c]imidazole-1,3-dione;

(7aS,6S)-2-(3,5-dichloro-phenyl)-6-(4-bromophenoxy)-tetrahydro-pyrrolo[1,2-c]imidazole-1,3-dione;

5-[2-(4-Chlorophenyl)ethyl]-2-(3,5-dichlorophenyl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione;

7-[2-(4-Bromophenyl)ethyl]-2-(3,5-dichlorophenyl)-tetrahydro-imidazo[1,5-a]pyrazine-1,3-dione;

7-[2-(4-Bromophenyl)-1-methyl-2-oxo-ethyl]-2-(3,5-dichlorophenyl)-tetrahydro-imidazo[1,5-a]pyrazine-1,3-dione;

(7aS,6S)-4-{[2-(3,5-dichloro-phenyl)-1,3-dioxo-hexahydro-pyrrolo[1,2-c]imidazol-6-ylamino]-methyl}-benzonitrile;

(7aS,6S)-N-(4-cyano-benzyl)-N-[2-(3,5-dichloro-phenyl)-1,3-dioxo-hexahydro-pyrrolo[1,2-c]imidazol-6-yl]-acetamide;

(6R,7aS)- [6-(4-bromobenzyloxy)-2-(3,5-dichlorophenyl)-1,3-dioxo-tetrahydro-pyrrolo[1,2-c]imidazol-7a-yl]-acetic acid methyl ester;

5-[2-(4-Bromophenyl)-2-oxoethyl]-2-(3,5-dichlorophenyl)-tetrahydropyrrolo[3,4-c]pyrrole-1,3-dione;

2-(3,5-Dichlorophenyl)-5-naphthalen-2-ylmethyl-tetrahydropyrrolo[3,4-c]pyrrole-1,3-dione;

(7aS,6S)-2-(3,5-dichloro-phenyl)-6-(4-bromobenzoyloxy)-tetrahydro-pyrrolo[1,2-c]imidazole-1,3-dione;

10a-(4-Bromo-benzyl)-2-(3,5-dichloro-phenyl)-10,10a-dihydro-5H-imidazo[1,5-b]isoquinoline-1,3-dione;

(6S,7aS)- 6-(4-bromobenzyloxy) -2-(3,5-dichlorophenyl))-tetrahydro-pyrrolo[1,2-c]imidazole-1,3-dione; or (ii) a pharmaceutically-acceptable salt thereof.

15. A pharmaceutical composition for treating an inflammatory or immune disease comprising (a) at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable carrier or diluent.

16. A pharmaceutical composition for treating an inflammatory or immune disease comprising (a) at least one compound according to claim 9, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable carrier or diluent.

17. A pharmaceutical composition comprising (i) at least one compound of claim 1 or a pharmaceutically acceptable salt thereof; (ii) one or more second compositions effective for treating an inflammatory or immune disease; and (iii) a pharmaceutically-acceptable carrier.

18. A method of treating an inflammatory or immune disease comprising administering to a mammal in need of such treatment a therapeutically-effective amount of a composition according to claim 15.

19. A method of inhibiting a Leukointegrin/ICAM-associated condition which comprises administering to a patient in need thereof an effective amount of a compound of claim 1.